REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 1-41 are pending after entry of the amendments set forth herein.

Claims 24-29 and 35-41 are currently withdrawn from examination.

Claims 1-23 and 30-34 were examined. Claims 1-23 and 30-34 were rejected.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

No new matter has been added.

The Telephone Interview

Applicants wish to extend their appreciation to the Examiner for the courtesy provided to Applicants' representative during the telephone interview of December 20, 2006. During the interview, the Examiner requested submission of disclosure documents as some evidence that it is known to examine differential expression levels of diseased tissue samples relative to a reference tissue sample for drug discovery. The Examiner further requested clarification of the distinction between the claimed phenotypic/genotypic signatures and the claimed phenotypic signature. Finally, the Examiner indicated that a search had not turned up disclosure of generation of in-phase and out-of-phase signatures.

This account is believed to be a complete and accurate summary of the interview as required by 37 C.F.R. § 1.133. If the Examiner believes that this summary is inaccurate or incomplete, Applicant respectfully requests that the Examiner point out any deficiencies in his next communication so that Applicant can amend or supplement the interview summary.

The Office Action

Claims Rejected Under 35 U.S.C. Section 112, First Paragraph

In the Official Action of October 12, 2006, claims 1-23 and 30-34 were rejected under 35 U.S.C.

Section 112, first paragraph as failing to comply with the written description requirement. The Examiner asserted that the claims contain subject matter which was not described in a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner asserted that "one of skill in the art cannot envision the detailed sequences of differential expression levels for the genus of disease processes. The specification does not provide any example, working or otherwise of differential gene sequence expression indicative of the genus of disease processes." The Examiner further asserted that the genus of disease processes includes many diseases known to or suspected of having a genetic association, however the identification of the genus of genes whose expression levels correlate with a disease and whose change would indicate treatment efficacy has not been accomplished for the wide genus of disease processes. The Examiner asserted that the specification does not disclose a representative number of species of differential expression levels of diseased processes such that one of [ordinary] skill in the art would envision that applicant had possession of the full scope of the claimed invention.

In response, Applicant respectfully submits that the invention is not directed to, and does not claim detailed sequences of differential expression levels for the genus of disease processes. In fact, the invention is not directed to identifying or discovering detailed sequences of differential expression levels for any disease, let alone the genus of diseases. Rather, the invention is directed to screening a combination of treatments to specifically target a disease process. In this regard, the claimed invention uses probes that are already known to be markers for a specific disease process, and screens treatment of diseased tissues diseased by the disease process to identify combinations of treatments that are likely to be effective.

Muraca, U.S. Patent Application Publication No. 2003/0049701, which was cited by the Examiner in the Office Action, discloses that the expression or form of a gene product can be used as a marker if it appears characteristically when a phenotype such as disease is observed. Muraca further discloses that numerous gene products have been shown to participate in or to be associated with human disease, and their measurement can provide diagnostic and prognostic tools to the clinician, see page 1, paragraph [0004]. Muraca notes that a range of levels of expression of a gene product might be associated with a phenotype A in which a cancer cell is relatively differentiated and respects its normal tissue boundaries, while an overlapping range of levels of expression may be associated with a phenotype B in which a cancer cell is relatively undifferentiated, but has not yet metastasized, and that it is difficult to make an accurate prognosis at the overlapping boundaries between phenotypes. Muraca

further notes that this situation is complicated by the fact that a disease, such as cancer, represents the interactions of multiple genes, each of which may be expressed at varying levels.

Applicant respectfully submits that this complication presents itself with many different types of disease, and the present invention addresses correlation in gene expression levels in diseased tissues, and treatment response values measure from the diseased tissues when treated with various different treatments. The present invention does not claim a genus of genes whose expression levels correlate with a disease process. Rather, the present invention correlates expression levels of genes whose expression levels are impacted by a disease process, with treatment response values after treating diseased tissues with various treatments.

In response to the Examiner's request during the telephone interview of December 20, 2006, Applicant is submitting herewith documents in an Information Disclosure Statement disclosing examples of genetic markers for various types of diseases to evidence that genetic markers for many types of diseases are currently known. The article titled "Exonhit Therapeutics presents at SG Cowen Annual Health Care Conference in Boston, Mar 7, 2002 discloses that well-defined disease genetic markers are known for neurodegenerative diseases and cancer. Thayer, "Biomarkers Emerge", Chemcial & Engineering News, vol. 81, no. 30, pp. 33-37, July 28, 2003 notes that Avalon has taken about 2000 genes and generate gene expression profiles of all know or potential anticancer agents to create a transcriptional structure-activity relationship database.

Accordingly, Applicant respectfully submits that genetic markers for various diseases were known at the time of the filing of the present invention. Further, Applicant reiterates that the present invention is not claiming any specific genetic markers, sets of genetic markers or a genus of genetic markers or genus of genes whose expression levels correlate with a disease and whose change would indicate treatment efficacy. Applicant further submits that the methods claimed in the present invention can be practiced with other genetic markers as they become available. Still further, Applicant respectfully submits that a specific set of genetic markers need not even be identified, as it is scientifically possible and commercially feasible to genotype (interrogate) over 1.5 million genetic variants (single nucleotide polymorphisms or SNPs) in each sample's genome within a whole genome association study. This number of variants results in a map of the human genome with a genetic marker approximately every 2000 bases. As a resulting it is possible to find a correlation with genetic markers within the causative gene or regulatory element, or very close to it.

In view of the above amendment and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1-23 and 30-34 under 35 U.S.C. Section 112, first

paragraph as failing to comply with the written description requirement, as being inappropriate.

Claims Rejected Under 35 U.S.C. Section 103(a) (Muraca in view of Glinskii)

Claims 1-4, 6-22 and 30-33 were rejected under 35 U.S.C. Section 103(a) as being unpatentable over Muraca, U.S. Publication No. 2003/0049701 in view of Glinskii, U.S. Publication No. 2004/0053317. The Examiner asserted that this application currently names joint inventors. Applicant respectfully traverses, as only one inventor is named in this application.

The Examiner asserted that Muraca teaches oncology arrays upon which samples from patients treated with chemotherapy, etc. may be assayed, and the Muraca also teaches guiding treatment based on the comparative levels of one or more cell-growth related polypeptides. The Examiner further noted that Muraca discloses a computer-assessable file regarding a collection of information regarding a tissue sample, which the Examiner interpreted to meet the recitation of remote transmission of data.

The Examiner admitted that Muraca does not disclose performing a clustering operation based on phenotypic or genotypic signatures. The Examiner asserted that Glinskii teaches the use of Affymetrix arrays for assay gene expression, and teaches the use of clustering methods to analyze gene expression profiles. The Examiner further asserted that Glinskii teaches that clinically relevant genetic signatures can be found by searching for clusters of co-regulated genes.

The Examiner asserted that it would have been obvious to have made and used a method for screening a combination of treatments to specifically target a disease process comprising performing a clustering operation based on the phenotypic/genotypic signatures.

Even if it would have been obvious to combine the references as suggested by the Examiner, which Applicants do not necessarily agree that it would have been obvious, the resultant combination would still not meet the limitations of the present claims. Claim 1 recites providing a phenotypic/genotypic signature for each feature that measures differential expression for the diseased tissues being studied. Thus a phenotypic/genotypic signature includes a differential expression level for a particular feature for each of the diseased tissue samples measured. When the diseased tissues are treated by a treatment, a treatment response value for each of the diseased tissues is measured, in response to the treatment applied. A treatment response value measures a phenotypic property of the diseased tissue, such as inhibition of tumor growth, reduction (or increase) of expressed levels of proteins that are produced in the disease process, etc. A phenotypic signature is provided for each treatment, with each phenotypic signature including a treatment response value for each of the diseased

tissue samples treated and measured. The differential expression signatures (phenotypic/genotypic) signatures are then clustered with the phenotypic signatures of the treatment-response values to select treatments.

Muraca discloses use of oncology tissue microarrays that have a plurality of sublocations, each sublocation comprising a cell or tissue sample having at least one known biological characteristic which is stably associated with a substrate at the sublocation. The plurality of sublocations comprises cancerous tissue at different neoplastic stages, see paragraph [0072]. A microarray may include a control microarray (containing a control sample) and a test sample for comparison with the control sample, see paragraph [0077]. Sublocations on the array comprise different types of abnormal tissues, e.g., brain tumor, pituitary tumor, cancerous eye tissue, etc., see paragraph [0085]. Muraca determines a molecular profile of a test sample and then compares this profile with the molecular profile of a set of microarray samples, in order to classify the test sample as to progression of disease, etc., see paragraph [0204]. Paragraph [0207] further describes that a processor can be used to analyze relationships between stored data and the data relating to the test tissue using regression, decision trees, neural networks, fuzzy logic and combinations thereof. However, this analysis is done to try and match relationships between the test tissue data and previously classified data, to try and determine a classification of the test tissue. Paragraph [0210] describes assaying the expression or form of a cancer-specific marker. The expression characteristics of cancer-specific markers are determined in test samples and compared to the expression characteristics of the markers in any of the previously classified and stored oncology arrays. Paragraph [0264] describes using a panel of cell and/or tissue samples representing a plurality of different stages of cancer used to generate sublocations on an oncology microarray, for use in predicting the prognosis of a given cell or tissue sample. Paragraph [0273] discloses that a microarray comprises samples from a drug-treated patient and samples form an untreated diseased patient and/or from a healthy patient.

Expression profiles of diagnostic molecules of drug treated diseased patients are compared with expression profiles of diagnostic molecules of a healthy patient and a drug is identified as useful for further testing when the expression pattern in the test sample is substantially the same as the expression pattern within the healthy tissue. Thus, Muraca does not compare phenotypic response signatures of diseased tissues with signatures of differential expression levels of the diseased tissues when untreated. Muraca's method is quite different, in that Muraca compares measurements of treated diseased tissues with profiles of healthy tissues.

Glinskii describes clustering analysis of differential gene expression across clinical and

experimental data sets, paragraph [0410]. Paragraph [0413], referred to by the Examiner, relates to discovery and validation of the prostate cancer recurrence predictor algorithm.

Neither Muraca nor Glinskii discloses or suggests generating a phenotypic signature representing the treatment-response values of each of the diseased tissue samples; doing this for multiple phenotypic signatures, performing a clustering operation based on the phenotypic/genotypic signatures of the differential expression levels and the phenotypic signatures of the treatment-response values together, or selecting treatments by identifying the treatment-response phenotypic signatures caused by those treatments, and which are clustered with phenotypic signatures representing differential expression levels representative of the diseased tissue samples.

Neither Muraca nor Glinskii compares phenotypic response signatures of diseased tissues with signatures of differential expression levels of the diseased tissues when untreated.

Further, neither Muraca nor Glinskii discloses, teaches or suggests labeling the phenotypic/genotypic signatures as "in phase" and generating "out of phase" signatures, as recited in claims 5, 23, 34 and 41.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10030208-1.

Respectfully submitted,

Date: 1/9/07

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